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(54) Title: METHOD OF PREPARATION OF SILDENAFIL

(57) Abstract: A method of preparation of sildenafil, i.e. 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl) phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazole[4,3-d]pyrimidin-7-one of formula (I) comprises the reaction of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula (II) and 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide of formula (III). The starting compound and the intermediate compound useful in the said method are new.

# Method of preparation of sildenafil

The object of the invention is a method of preparation of sildenafil, i.e. 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazol[4,3-d]pyrimidin-7-one, as well as novel starting and intermediate compounds useful in the method.

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, known under non-proprietary name sildenafil, is a potent and selective inhibitor of phosphodiesterase of cyclic guanozine-3',5'-monophosphate (cGHP PDE), active in many therapeutic areas, such as treatment of cardiovascular disorders, particularly in the treatment of male erectile dysfunction.

Sildenafil as a chemical compound is known from European Patent No. EP 0463756, wherein a method of its preparation has also been disclosed.

The abovementioned method consists in condensation of o-ethoxybenzoic acid chloride with 4-amino-1-methyl-3-n-propyl-pyrazole-5-carboxyamide in dichloromethane, and then cyclization of the resulting 4-(2-ethoxybenzamide)-1-methyl-3-n-propyl-carboxyamide in an alkaline solution of 30% hydrogen peroxide to yield the

corresponding derivative of 7H-pyrazole[4,3-d]pyrimidin-7-one. The derivative is subjected to chlorosulfonation under nitrogen to yield 5-(5-dichlorosulfonyl-2-ethoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, which is then condensed with N-methylpiperazine to yield sildenafil (overall yield of approx. 27%).

In European Patent No. EP 0812845 a new, enhanced method of preparation of sildenafil is disclosed, consisting in preparation of 5-chlorosulfonyl-2-ethoxybenzoic acid and converting it into 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzoic acid. The acid is then condensed with 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide in the presence of N,N'-carbonyldiimidazole, and the resulting 4-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzamido]-1-methyl-3-n-propylpyrazolo-5-carboxyamide is cyclized in an alkaline, neutral or acid solution to yield sildenafil (Yield: about 47%).

It has now been found that sildenafil can be prepared with the higher yield while employing a smaller number of steps than that of methods known in the art, using new starting compounds, not yet described in the literature, and utilizing a new intermediate compound, the said compounds also constituting the essential of the invention.

Simultaneously, it has been found, that, when necessary, sildenafil can be obtained without isolating an intermediate compound in a one-step reaction, using the same new starting compounds.

The method of preparation of 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazole[4,3-d]pyrimidin-7-one of formula (I) comprises the reaction of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula (II) and 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide of formula (III).

In a preferred embodiment of the invention the reaction consists in that equimolar amounts of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula (II) and 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide of formula (III) are subjected to conjugation in an organic solvent at temperature from 50 to 100°C for 2 to 12 hours, and then the intermediate compound - 5-propyl-4-{[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)-benzylidene]-amino}-2-methyl-2H-pyrazole-3-carboxyamide of formula (IV) is dissolved or suspended in an organic solvent and heated at temperature from 100 to 180°C at 1.5-4.0 molar excess of sodium hydrogen sulfite.

The conjugation of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde with 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide is carried out in a

solvent selected from the group consisting of: aromatic hydrocarbons, tertiary amides of lower $C_{1-3}$ carboxylic acids, halogen derivatives of benzene, N-alkylpyrrolidone-2, dimethyl sulfoxide, sulfolane, alkylcarboxylates and mixtures thereof.

The intermediate compound of formula (IV) is dissolved or suspended in a solvent selected from the group consisting of: tertiary amides of lower $C_{1-5}$ carboxylic acids, halogen derivatives of benzene, sulfolane, dimethyl sulfoxide or N-alkylpyrrolidones-2.

The preferred solvent for the intermediate compound is dimethylformamide, dimethylacetamide, dimethyl sulfoxide, sulfolane or N-methylpyrrolidone-2.

A type of the solvent is chosen depending on conditions of the reaction, according to rules known to persons skilled in the art. 5-Propyl-4-{[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)-benzylidene]amino}-2-methyl-2H-pyrazole-3-carboxyamide, prepared at the conjugation step, is a new compound and as such it is within the scope of the invention.

In another preferred embodiment of the invention sildenafil is prepared without isolating the intermediate product and it consists in that 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula (II) is subjected to cyclocondensation with 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide of formula (III) in a solvent, in the presence of

condensing agent, then the reaction mixture is neutralized and the resulting product is isolated from the mixture.

As a condensing agent sodium hydrogen sulfite may be used in the amount from 1.5 to 3 moles per 1 mole of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl) benzaldehyde.

The reaction is carried out at temperature from 110 to 170°C for 2 to 50 hours.

The reaction of cyclocondensation is carried out in an organic solvent selected from the group consisting of: aromatic hydrocarbons , tertiary amides of lower $C_{1-3}$ carboxylic acids, chlorine derivatives of benzene, N-alkylpyrrolidones-2, dimethyl sulfoxide, sulfolane, $C_{3-12}$ alkanols, $C_{3-12}$ cycloalkanols, $C_{4-10}$ cycloalkanones and mixtures thereof.

The reaction is preferably carried out in dimethylformamide, dimethylacetamide, toluene, xylene, chlorobenzene, 1.2-dichlorobenzene, sulfolane, N-methylpyrrolidone-2 or dimethyl sulfoxide.

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazole[4,3-d]pyrimidin-7-one, prepared by the method of the invention, is isolated and purified by methods known in chemistry. As a matter of example, preliminary dilution or concentration of the reaction mixture is used, and then the product is isolated by filtering

off, extraction and optionally crystallization from a solvent. Alternatively, the compound of formula 1 may be isolated and/or purified by known chromatographic techniques.

The overall yield of pure 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazole[4,3-d]pyrimidin-7-one - recalculated to reagents used in the cyclocondensation - amounts to about 85%.

The starting compound for the cyclocondensation reaction - 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula 2 is a new compound, not yet described in the literature.

2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde can be obtained by a method analogous to known preparation methods of compounds of that type.

For example, 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde is prepared in the reaction of N-sulfonation of 2-ethoxy-5-chlorosulfonylbenzaldehyde with equimolar amounts of 1-methylpiperazine. The N-sulfonation is carried out in the presence of triethylamine at temperature within the range: 10 to 35°C, preferably 15 to 20°C, in a solvent selected from the group consisting of: halogenated derivatives of lower hydrocarbons, $C_{3-6}$ aliphatic ketones and water. The preferred solvent is dichloromethane or acetone.

2-Ethoxy-5-chlorosulfonylbenzaldehyde can be obtained e.g. from salicylaldehyde by alkylation with diethyl sulfate to 2-ethoxybenzoic aldehyde, and then by converting it with the use of ethyl orthoformate into diethylacetal, which is then subjected to chlorosulfonation with simultaneous deprotecting of aldehyde group. At chlorosulfonation step, performed at temperature from -10 to +10°C, a 20 to 50-fold molar excess of chlorosulfonic acid is generally used. Alternatively, chlorosulfonation is carried out using a mixture of 1 molar equivalent of thionyl chloride and 4-10 molar equivalents of chlorosulfonic acid, maintaining temperature below 30°C, and then the reaction is allowed to be completed at room temperature.

The starting aminopyrazole can be prepared by a method known to persons skilled in the art i.e. by reduction of the corresponding nitropyrazole, for example by hydrogenation in the presence of palladium or nickel as a catalyst or by means of stannous chloride in ethanol. After isolation from the solution the resulting aminopyrazole can be used immediately in the conjugation reaction with the aldehyde.

The invention makes it possible to prepare sildenafil with high yield i.e. over 85% (recalculated to the starting 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde). The method according to the

invention does not involve complex technical operations and allows to use easily available starting compounds.

The invention is further illustrated by the following examples of invention embodiments.

Example 1.

Ethyl 1-methyl-3-n-propyl-pyrazole-5-carboxylate

Mixture of ethyl 3-n-propyl-pyrazole-5-carboxylate (12.05 g; 0.066 mole) and dimethyl sulfate (8.4 g; 0.066 mole) was heated at temperature 90°C for 2.5 hours. The content of a flask was then dissolved in dichloromethane (50 ml) and the resulting solution was washed with a saturated solution of $NaHCO_3$. The organic layer was separated and dried with anhydrous $MgSO_4$. After evaporation of the solvent, 10.5 g (82%) of crude product was obtained and then used in the subsequent step without further purification.

Example 2.

1-Methyl-3-n-propyl-pyrazole-5-carboxylic acid

Ethyl 1-methyl-3-n-propyl-pyrazole-5-carboxylate (10.1 g; 0.05 mole) was suspended in 6N aqueous solution with NaOH (25 ml; 0.15 mol). The mixture was heated for 2 hours at temperature 80°C, diluted with water (25 ml) and acidified with concentrated hydrochloric acid (12.5 ml). The resulting white

precipitate was filtered off and dried to yield 6.15 g (71%) of the pure title compound.

M.p. 148-150°C.

Example 3.

1-Methyl-4-nitro-3-n-propyl-pyrazole-5-carboxylic acid

1-Methyl-3-n-propyl-pyrazole-5-carboxylic acid (6.05 g; 0.036 mole) was added in portions to a mixture of fuming sulfuric acid (6.5 ml) and fuming $HNO_3$ (5.5 ml) maintaining the temperature below 60°C. Upon dosage, the resulting mixture was heated at 70°C for 12 hours and then cooled to room temperature. Then, the flask content was poured onto ice/water (30 g) to yield a white crystalline product (6.02 g; 78.5%).

M.p. 124-126°C.

Example 4.

1-Methyl-4-nitro-3-n-propyl-pyrazole-5-carboxyamide

1-Methyl-4-nitro-3-n-propyl-pyrazole-5-carboxylic acid (11.3 g; 0.05 mole) was added to thionyl chloride (50 ml) and the resulting mixture was heated for 3 hours. After that the flask content was cooled and an excess thionyl chloride was evaporated under vacuum. The oily residue was dissolved in acetone (50 ml) and the resulting solution was cautiously added to a mixture of ice (50 g) and concentrated ammonia solution (50 ml). The resulting precipitate was washed with

water to yield 9.05 g of white crystalline product (Yield 80%).

M.p. 139-142°C.

Example 5.

4-Amino-1-methyl-3-n-propyl-pyrazolecarboxyamide

A) Reduction with $SnCl_2$

1-Methyl-4-nitro-3-n-propyl-pyrazole-5-carboxyamide (3.45 g; 0.016 mole) and stannous chloride dihydrate (18.4 g; 0.08 mole) was suspended in ethanol and the mixture was heated at reflux for 3 hours. The resulting solution was cooled to room temperature and alkalized to pH 10 with 2N NaOH. The suspension was extracted several times with dichloromethane (4 x 70 ml), the organic layers were combined, dried with anhydrous $MgSO_4$ and evaporated. The oily residue was triturated with diethyl ether to yield 2.65 g of cream-colored product (Yield 91%).

M.p. 99-101°C.

B). Catalytic reduction

Mixture of 1-methyl-4-nitro-3-n-propyl-pyrazole-5-carboxyamide (23.77 g; 0.112 mole) and 10% palladium-on-carbon (4.75 g) in ethyl acetate (210 ml) was subjected to hydrogenation under pressure (3.5 atm) at temperature 50°C for 4-5 hours. The cooled reaction mixture was filtered through Celite, and then a

filtration cake was washed with ethyl acetate (30 ml). The filtrate and washings were combined, and after evaporating solvent under vacuum, 4-amino-1-methyl-3-n-propyl-pyrazolecarboxyamide (19.2 g; 94%) was obtained. M.p. 98-101°C.

Example 6.

2-Ethoxybenzoic aldehyde

To a suspension of salicylaldehyde (12.21 g; 0.1 mole) and 2N aqueous sodium hydroxide solution (55 ml) diethyl sulfate (13.1 ml; 0.1 mole) was slowly added drop by drop under stirring, while maintaining temperature below 40°C. The resulting mixture was stirred for 5 minutes and then further amounts of 2N aqueous sodium hydroxide solution (27.5 ml) and diethyl sulfate (6.55 ml) were added. After stirring for 30 minutes at temperature 40-45°C, the resulting mixture was cooled to 20°C and extracted with diethyl ether (3 x 400 ml). After concentration of the organic layer, 15 g of crude product was obtained, which was distilled under reduced pressure (2.1 hPa) to yield the pure product; b.p. 95-97°C (10.67 g, Yield 71.1%).

Example 7.

Diethylacetal of 2-ethoxybenzoic aldehyde

Ethyl orthoformate (25.8 g; 0.174 mole) was added dropwise under stirring to 2-ethoxybenzoic aldehyde

(23.75 g; 0.158 mole). Upon thorough mixing of reagents, during which the temperature has risen to 40°C, ethanol (22.16 g; 0.48 mole) and ammonium chloride (0.33 g; 0.006 mole) were added. The reaction mixture was heated slowly to temperature 60°C and then stirred for 3.5 hours. After that, the flask content was cooled, concentrated and $NH_4Cl$ was filtered off. The obtained crude product (35.4 g) was distilled under reduced pressure (0.8 hPa) at temperature 88-93°C to yield approx. 30 g of the pure product (Yield: approx. 84 %).

Example 8.

2-Ethoxy-5-chlorosulfonylbenzaldehyde

To stirred and cooled to -5°C chlorosulfonic acid (37.9 g; 0.325 mole), diethylacetal of 2-ethoxybenzoic aldehyde (1.6 g; 0.007 mole) was added dropwise during 1.5 hours. Upon completion of dosage, the reaction mixture was left at temperature -5 to +5°C for 2 hours, while continuing stirring. Then, it was poured onto ice with water. The resulting precipitate was filtered off and washed with water. 13.8 g of the precipitate was obtained (Yield: 78%).

M.p. 47-50°C.

Example 9.

2-Ethoxy-5-(4-methylpiperazin-1-yl-sulfonyl)benzaldehyde

To a mixture of 1-methylpiperazine (4.6 g; 0.046 mole) and triethylamine (4.6g; 0.0455 mole) in methylene chloride (57 ml), 2-ethoxy-5-chlorosulfonylbenzaldehyde (11.45 g; 0.046 mole), diluted with methylene chloride, was added dropwise at temperature 15-20°C. After completion of dosage, the resulting mixture was stirred for further 2 hours. Then, the reaction mixture was washed with water and concentrated to yield the crude product. After crystallization from ethanol 12.6 g of the final product (Yield: approx. 95%) was obtained.

$^1$H-NMR ($CDCl_3$, 200MHz), δ (ppm): 1.48-1.60(t.3H, J=7.0Hz); 2.28(s.3H); 2.44-2.54(m.4H); 2.98-3.10(m.4H); 4.18-4.32(q.2H,J=7.0Hz); 7.07-7.15(d.1H,J=8.8Hz); 7.87-7.95(dd.1H,J=2.4Hz); 8.17-8.21(d.1H,J=2.4Hz); 10.50(s.1H).

Example 10.

5-Propyl-4-{[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)-benzylidene]amino}-2-methyl-2H-pyrazole-3-carboxyamide

2-Ethoxy-5-(4-methylpiperazin-1-yl-sulfonylbenzaldehyde (65 g; 0.208 mole) and 4-amino-1-methyl-3-n-propyl-pyrazolecarboxyamide (37.9 g; 0.208 mole) were heated in toluene at reflux. 3.5 ml of water

was received during 2 hours. The resulting mixture was heated for further 1 hour until the starting materials reacted completely. After cooling, the resulting precipitate was filtered off, washed with toluene and dried. Approx. 93 g (95%) of the title intermediate product was obtained.

$^1$H-NMR (DMSO-d6, 200MHz), δ (ppm): 0.92-1.03(t.3H,J=7.1Hz); 1.36-1.47(t.3H,J=7Hz); 1.57-1.77(m.2H0; 2.14(s.3H); 2.32-2.43(m.4H); 2.6-2.70(t.2H); 2.83-2.94(m.4H); 4.03(s.3H); 4.21-4.35(q.2H,J-7.1Hz); 7.36-7.44(d.1H,J=9.0Hz); 7.78-7.87(dd.1H,J=2.4); 7.94-8.01(m.1H); 8.03-8.10(m.1H); 8.13-8.17(d.1H,J=2.4); 8.92(s.1H).

Example 11.

5-[2-Ethoxy-5-(4-methylpiperazin-1-yl-sulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazole[4,3-d]pyrimidin-7-one (Method 1)

The intermediate compound of Example 10 (2 g; 0.0042 mole) and sodium hydrogen sulfite (0.655 g; 0.0063 mole) was suspended in dimethylacetamide (3.4 ml). The resulting mixture was heated for 6 hours. After cooling, 1.8 g (90%) of the title compound was isolated from the reaction mixture.

$^1$H-NMR (DMSO-d6, 200MHz), δ (ppm): 0.88-0.90(t.3H,J=7.3Hz); 1.28-1.38(t.3H,J=7.0Hz); 1.65-1.85(sex.2H,J=7.3Hz); 2.15(s.1H); 2.30-2.45(m.4H);

2.72-2.85(t.2H,J=7.8Hz); 2.85-2.96(m.4H); 4.15(s.3H); 4.15-4.28(q.2H); 7.38-7.42(d.1H); 7.79-7.87(m.2H); 12.21(s.1H).

Example 12

5-[2-Ethoxy-5-(4-methylpiperazin-1-yl-sulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazole[4,3-d]pyrimidin-7-one (Method 2)

A suspension of 2-ethoxy-5-(4-methylpiperazin-1-yl-sulfonyl)benzaldehyde (1.71 g; 0.00549 mole), 4-amino-1-methyl-3-n-propyl-pyrazolecarboxyamide (1 g; 0.549 mole) and sodium hydrogen sulfite (0.856 g; 0.0082 mole) in dimethylformamide was stirred for 3 hours at temperature 155°C. After isolation and purification of the crude product, 2.2 g of the product as a precipitate was obtained (Yield 84.6%).

$^1$H-NMR (DMSO-d6, 200MHz), δ (ppm): 0.88-0.90(t.3H,J=7.3Hz); 1.28-1.38(t.3H,J=7.0Hz); 1.65-1.85(sex.2H,J=7.3Hz); 2.15(s.1H); 2.30-2.45(m.4H); 2.72-2.85(t.2H,J=7.8Hz); 2.85-2.96(m.4H); 4.15(s.3H); 4.15-4.28(q.2H); 7.38-7.42(d.1H); 7.79-7.87(m.2H); 12.21(s.1H).

Patent claims

1. The method of preparation of 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazole[4,3-d]pyrimidin-7-one of formula (I) comprising the reaction of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula (II) and 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide of formula (III).

2. A method according to claim 1, wherein equimolar amounts of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula (II) and 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide of formula (III) are subjected to conjugation reaction in an organic solvent, at temperature from 50 do 100°C, for 2 to 12 hours, the resulting intermediate compound - 5-propyl-4-{[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)-benzylideneamino}-2-methyl-2H-pyrazole-3-carboxyamide of formula (IV) is isolated from the reaction mixture and after dissolving or suspending it in a solvent it is heated at temperature from 100 to 180°C with 1.5 to 4.0 molar excess of sodium hydrogen sulfite.

3. A method according to claim 2, wherein the conjugation step is carried out in a solvent selected from the group consisting of: aromatic hydrocarbons , tertiary amides of lower $C_{1-3}$ carboxylic acids, halogen derivatives of benzene, N-alkylpyrrolidones-2, dimethyl

sulfoxide, sulfolane, alkyl carboxylate and mixtures thereof.

4. A method according to claim 1 or 3, wherein an intermediate compound of formula (IV) is dissolved or suspended in a solvent selected from the group consisting of: tertiary amides of lower $C_{1-5}$ carboxylic acids, halogen derivatives of benzene, sulfolane, dimethyl sulfoxide and N-alkylpyrrolidones-2.

5. A method according to claim 2, wherein the intermediate compound of formula (IV) is dissolved or suspended in a solvent, which is dimethylformamide, dimethylacetamide, dimethyl sulfoxide, sulfolane or N-methylpyrrolidone-2.

6. A new compound of formula (II), which is 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde.

7. A new compound of formula (IV), which is 5-propyl-4-{[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)-benzylidene)amino]-2-methyl-2H-pyrazole-3-carboxyamide.

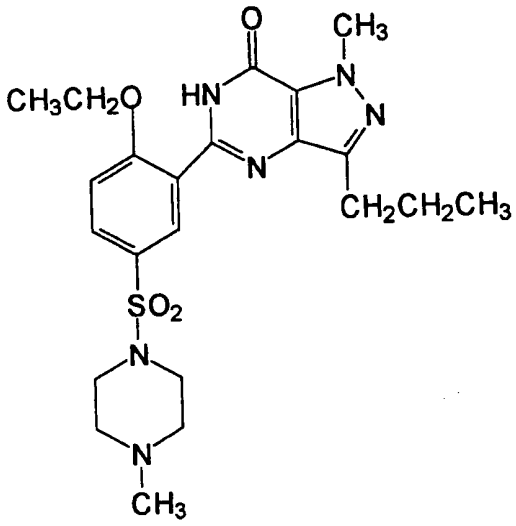
8. A method of preparation of sildenafil of formula (I), wherein 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde of formula (II) is subjected to one-step cyclocondensation reaction with 4-amino-1-methyl-3-n-propylpyrazole-5-carboxyamide of formula (III) in a solvent, in the presence of condensing agent at temperature from 110 do 170°C for 2 to 50 hours, the reaction mixture is neutralized and the resulting

product is isolated from the reaction mixture by a known method.

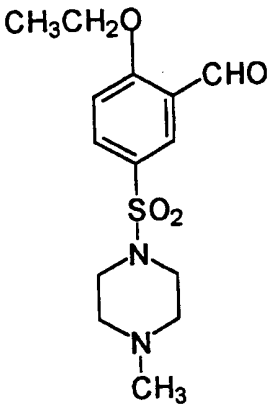
9. A method according to claim 8, wherein as a condensing agent sodium hydrogen sulfite is used in the amount of 1.5-3 moles per 1 mole of 2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)benzaldehyde.

10. A method according to claim 8, wherein the reaction is carried out in an organic solvent selected from the group consisting of: aromatic hydrocarbons, tertiary amides of lower $C_{1-3}$ carboxylic acids, chlorine derivatives of benzene, N-alkylpyrrolidones-2, dimethyl sulfoxide, sulfolane, $C_{3-12}$ alkanol, $C_{3-12}$ cycloalkanol, $C_{4-10}$ cycloalkanones and mixtures thereof.

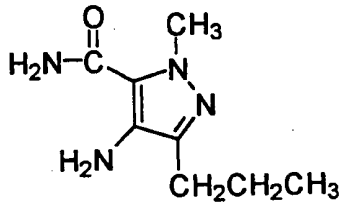
11. A method according to claim 8 or 10, wherein the reaction is carried out in dimethylformamide, dimethylacetamide, toluene, xylene, chlorobenzene, 1.2-dichlorobenzene, sulfolane, N-methylpyrrolidone-2 or dimethyl sulfoxide.



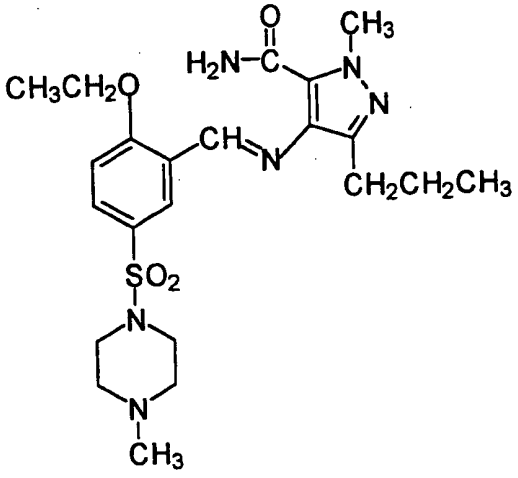
(I)



(II)



(III)



(IV)